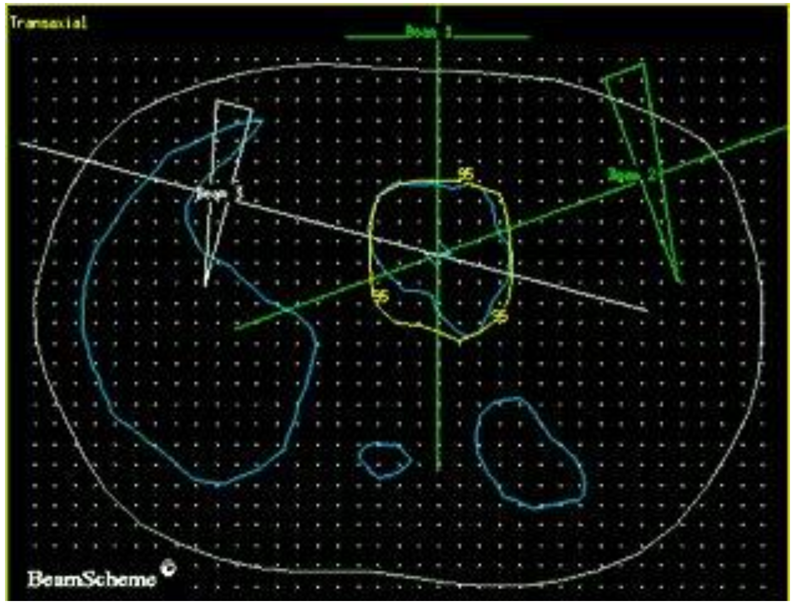
Radiothérapie par minifaisceaux

Yolanda Prezado
Nouvelles approaches in Radiotherapy (NARA)
Laboratoire Imagerie et Modélisation pour
la Neurobiologie et la Cancérologie
Campus d'Orsay, France

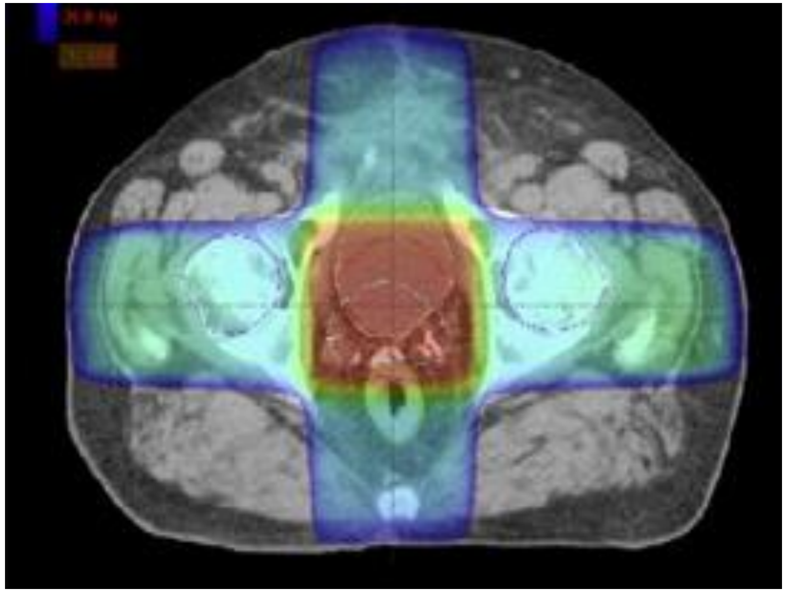
prezado@imnc.in2p3.fr

In the last decades

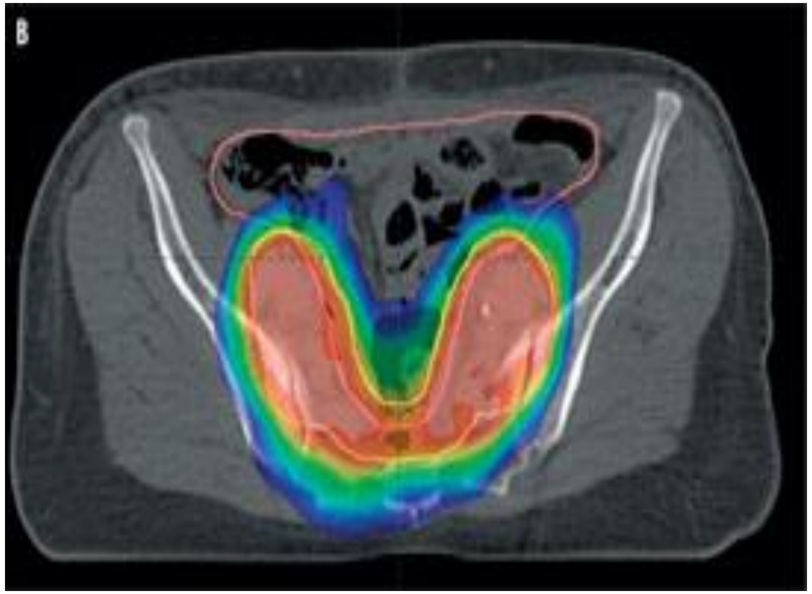
2D radiotherapy



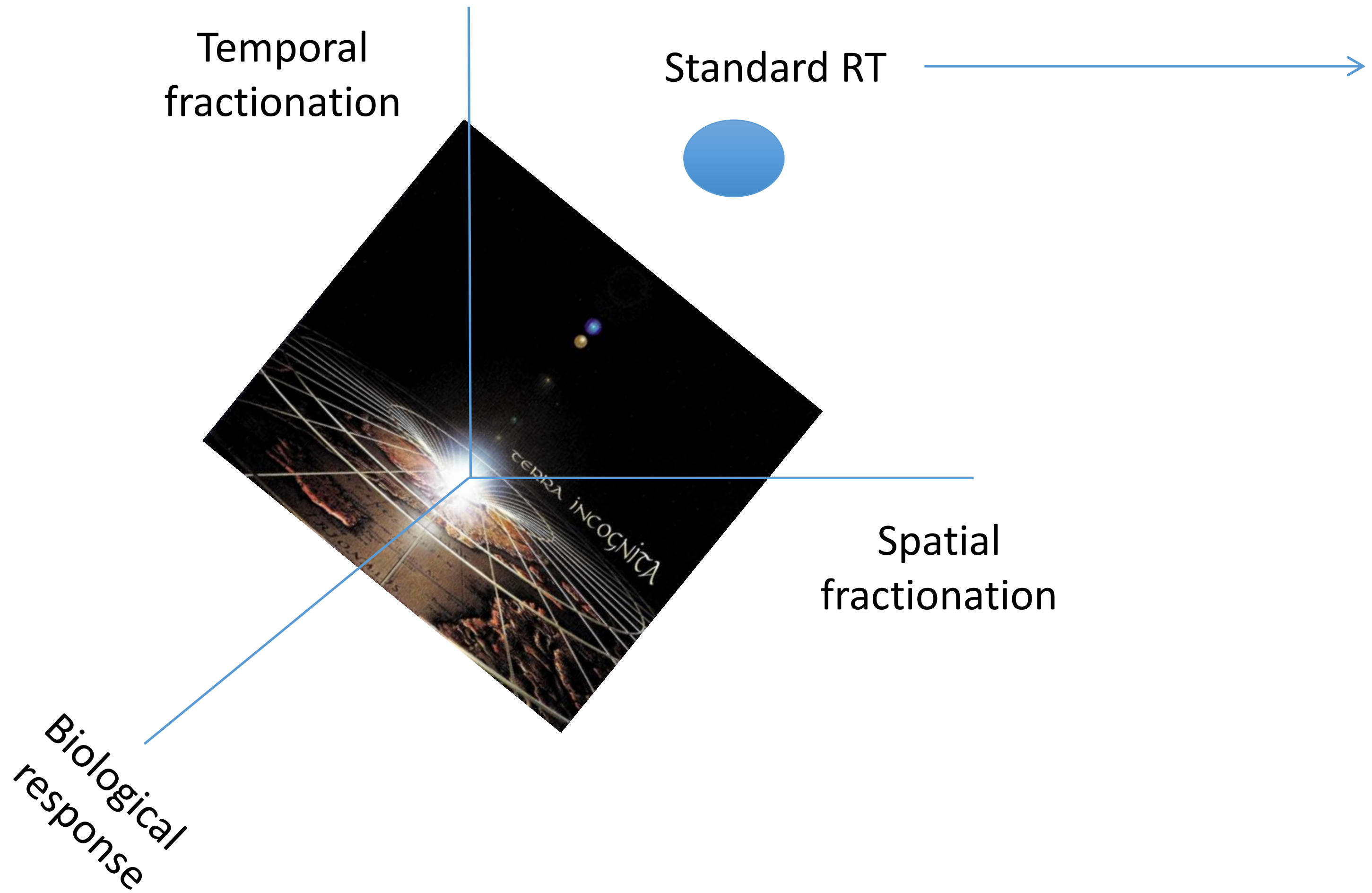
3D conformal radiotherapy



Intensity modulated RT



Radiotherapy: modeling biological response



- LINACS → MV photons/e- (95%)-protons-hadrons (5%)
- 2 Gy/session, 1 session per day, 5 days/week
- Dose rate~ 2 Gy/min
- Field sizes > cm^2
- Homogeneous dose distributions

Radiotherapy: modeling biological response

Tumor control probability

Normal tissue complication probability

Physical dose → **Biological dose**

↑

Biological effect of the radiation

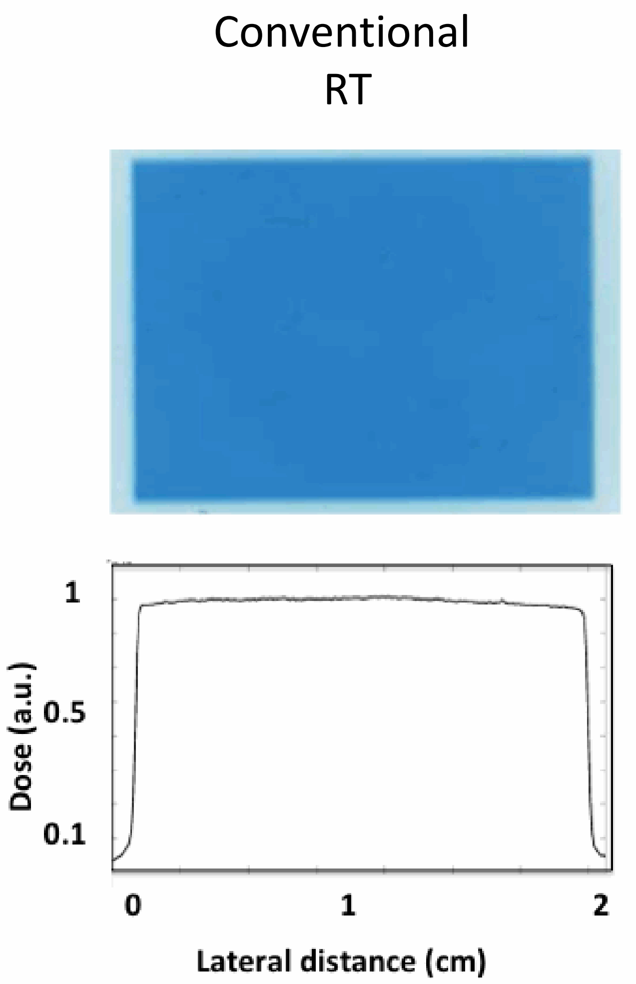
Physical parameters of irradiation

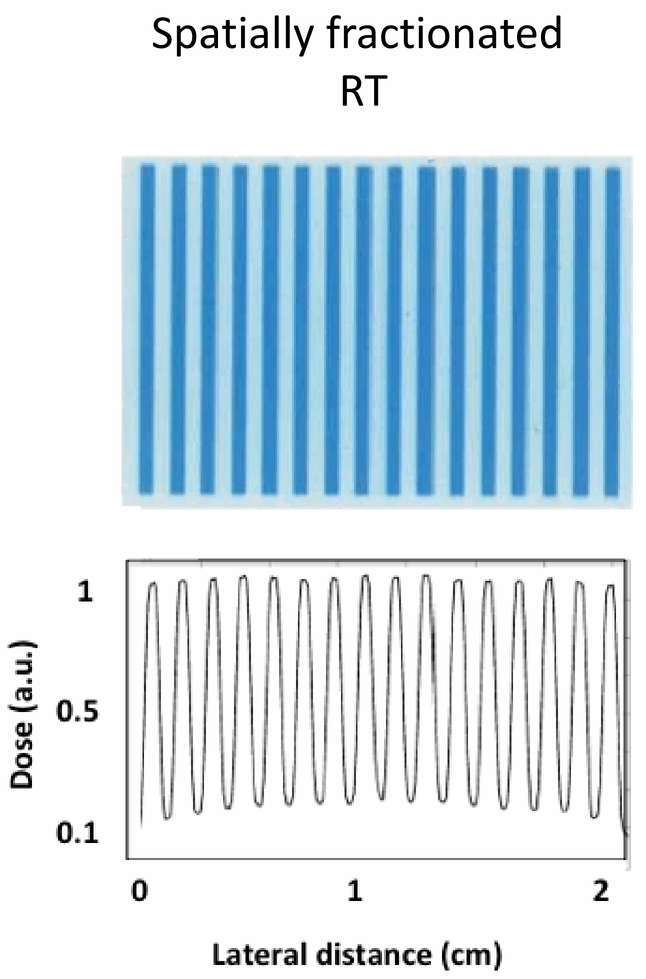
- Type of radiation
- Beam energy
- Delivery mode: dose rate, spatial and temporal distributions, etc.

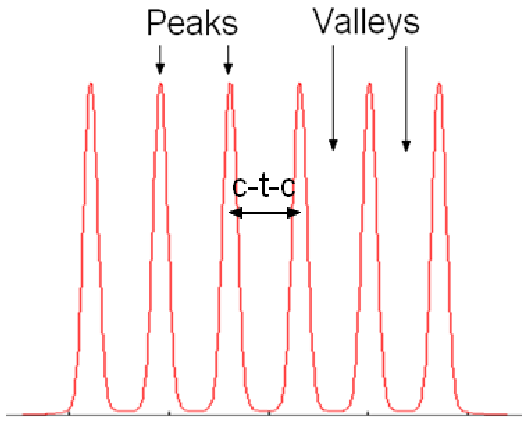
Biological factors

- Tumor type
- Tumor microenviroment
- Genetics

Spatial fractionation of the dose

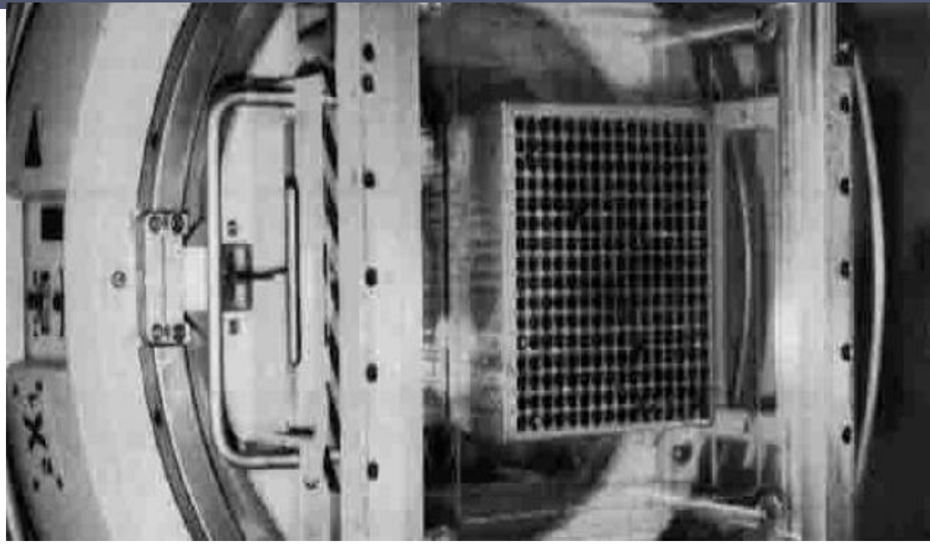






$$PVDR = \frac{D_{\text{peak}}}{D_{\text{valley}}}$$

RT techniques based on a spatial fractionation of the dose



GRID Therapy (few hospitals in the world)

1909 Alban Kohler used a "perforated screen" (grid)→ effect similar to treatment with small pencil beams.

Widely used in the 1950s as a way to reach tumors deep in the body with kilovoltage beams.

From the 70s GRID therapy with megavoltage radiation beams → palliation of selected, massive and bulky tumors

Improved response to RT and may possibly have cell killing effects outside the directly irradiated area

Beam sizes > 1 cm^2

PVDR from 2 to 5

Radiotherapy: modeling biological response

Tumor control probability

Normal tissue complication probability

Physical dose → **Biological dose**

Biological effect of the radiation

Physical parameters of irradiation

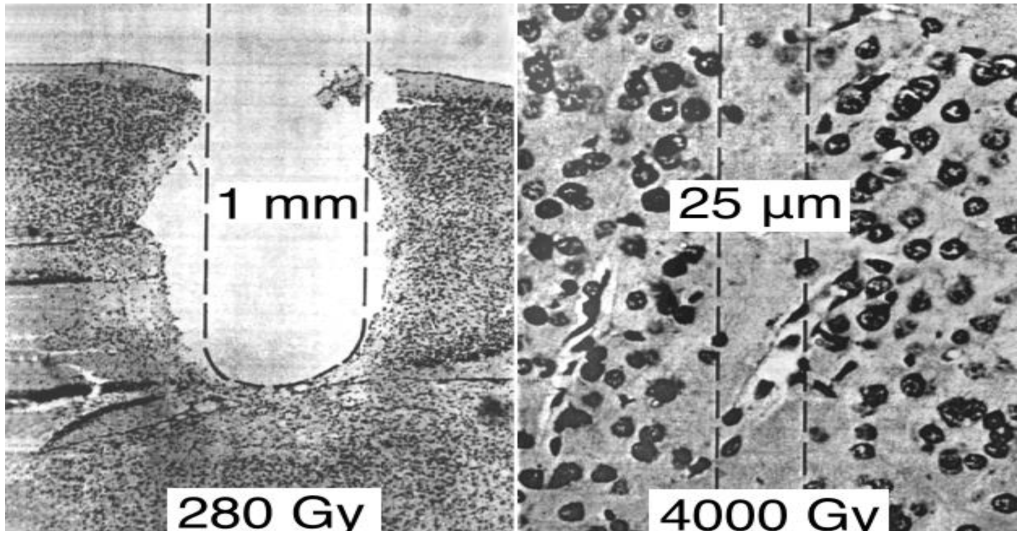
Type of radiation
Beam energy
Delivery mode: dose rate, spatial and temporal distributions, field size, etc.

Tumor type
Tumor microenviroment
Genetics

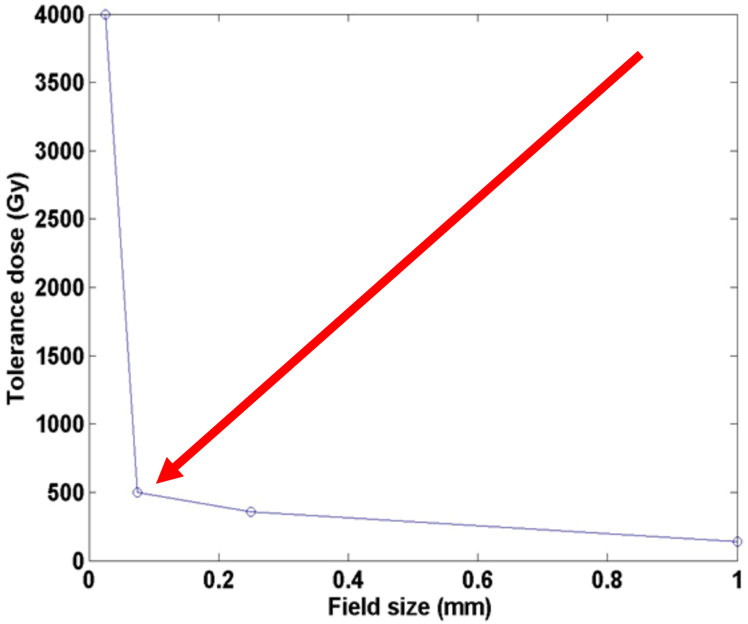
Biological factors

Field size

Dose-volume effect: the smaller the field size is, the higher the tolerance

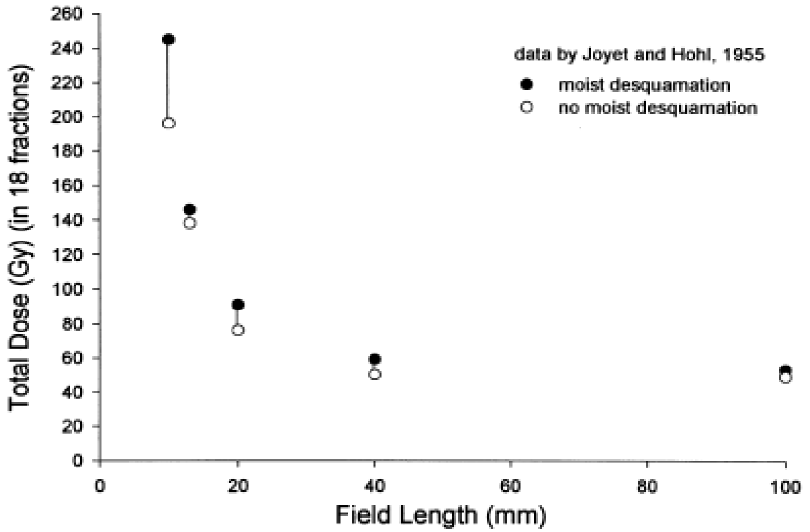


Zeman et al., Science (1959)

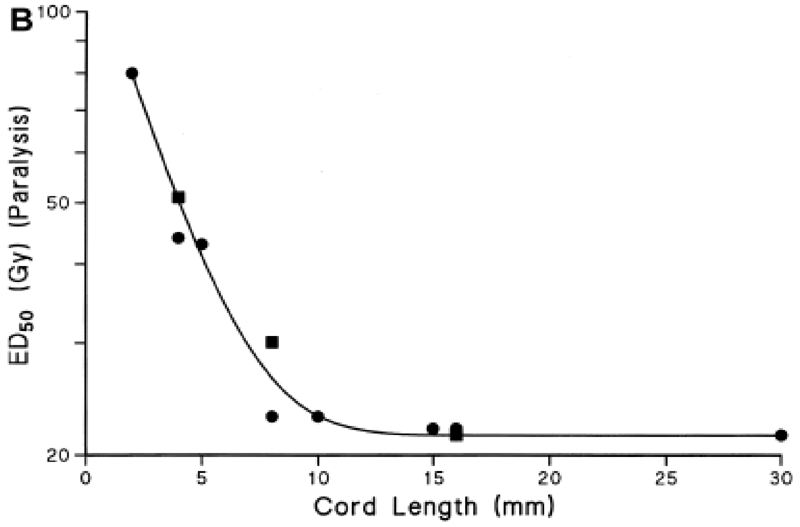


More recent examples with high energy photons

SKIN



SPINAL CORD



J.W. Hopewell, K.R. Trott / Radiotherapy and Oncology 56 (2000) 283-288

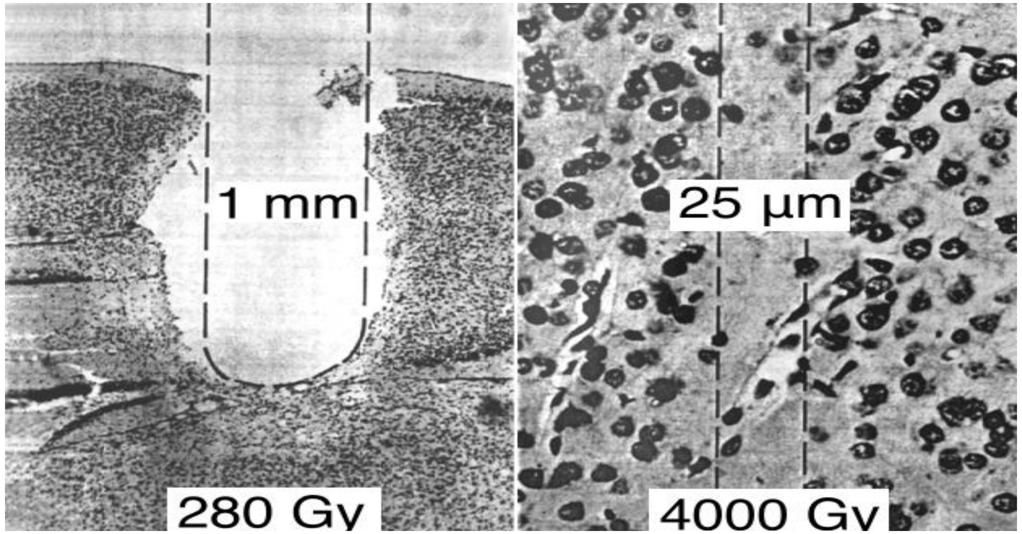
➢The stem-cell depletion hypothesis → for each organ exits a limiting critical volume, which can be repopulated by a single surviving stem cell and for which damage can be repaired by repopulation (Yaes & Kalend, 1988; Yaes et al, 1988).

Novel RT techniques based on “different” delivery modes

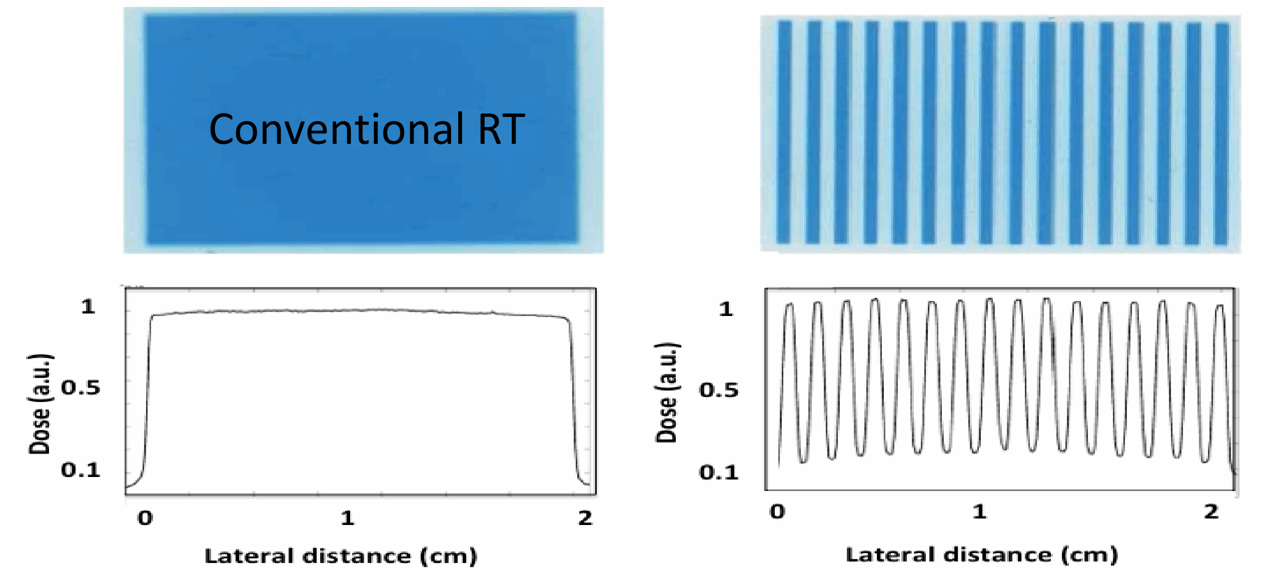
Combination

very small field sizes (< $1mm^2$) + Spatial fractionation of the dose

Dose-volume effects



Zeman et al., Science (1959)

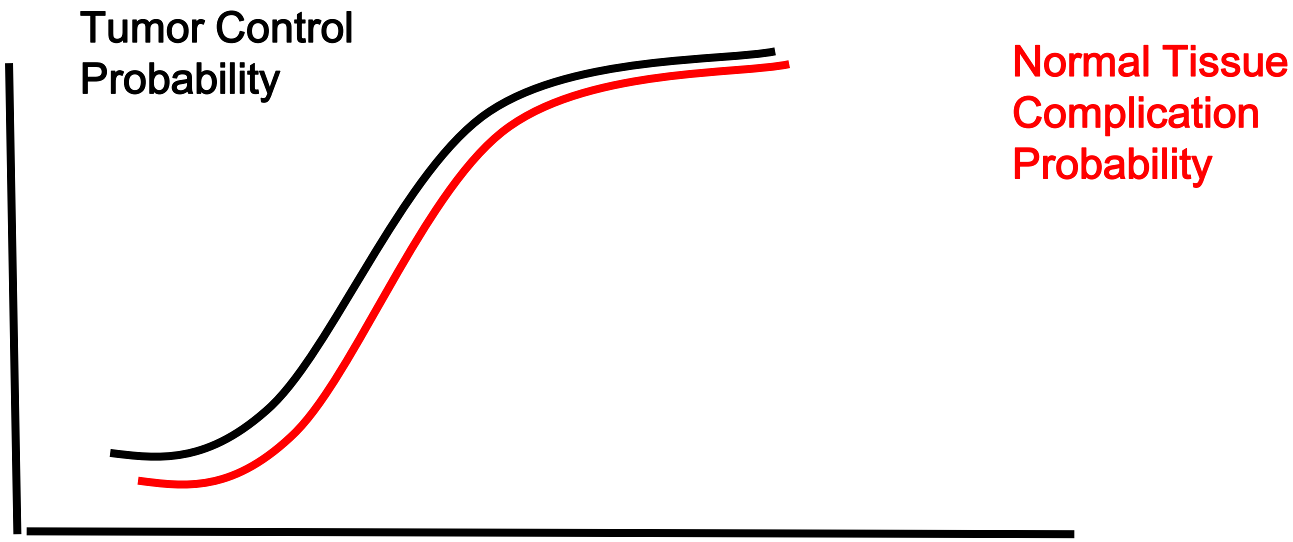


Novel RT techniques based on “different” dose delivery methods

Dose-volume effects→ exponential increase of healthy tissue tolerances

+

Spatial fractionation→ gain in healthy tissue recovery →increase of healthy tissue tolerances

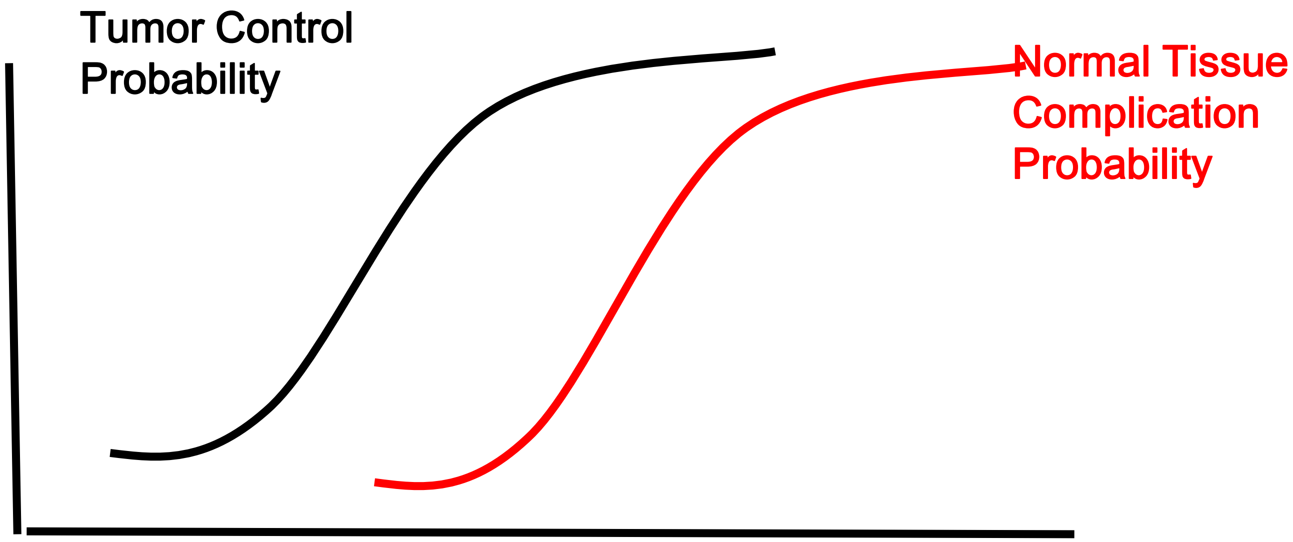


Novel RT techniques based on “different” dose delivery methods

Dose-volume effects→ exponential increase of healthy tissue tolerances

+

Spatial fractionation→ gain in healthy tissue recovery →increase of healthy tissue tolerances



Synchrotron micro and minibeam radiation therapy

Submillimetric field sizes (25 to 700 µm)
Interbeam separation (400 to 3500 µm)

Dose profiles consist of a pattern of peaks and valleys

Kilovoltage beams

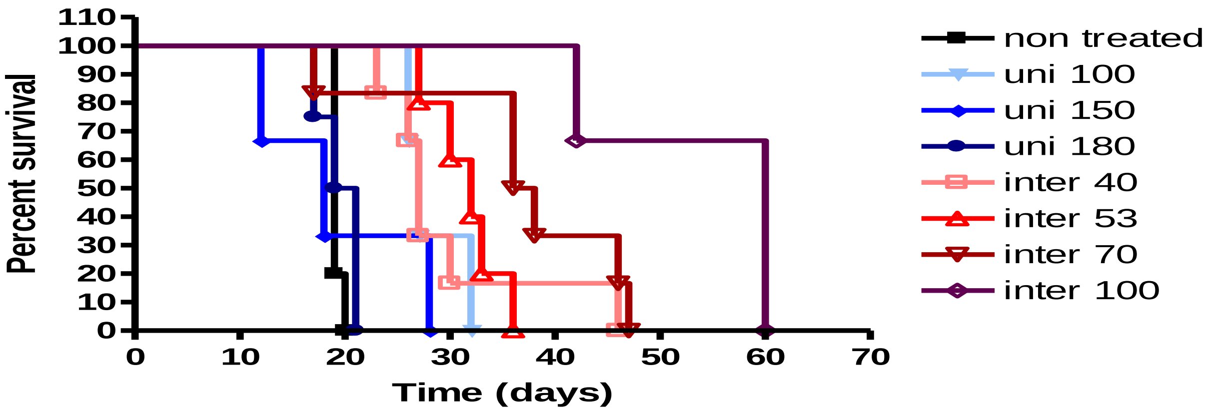
Minibeam Radiation therapy

High resistance of normal tissues

Doses as high as 100 Gy/session are still well-tolerated by the rat brain in comparison to 22 Gy in RT conventional

Prezado et al, Rad. Reseach 2015

A factor 3 increase in lifespan of glioma bearing rats



Prezado et al., J. Synchr. Rad. 2012

Biological effects not well understood

- Cell migration seems to be the responsable for tissue reparaison

- Differential effect normal-tumoral tissues

  - *Induction of denudation of tumor vessel endothelium, of a decrease in tumor blood volume as well as of tumor hypoxia.*

  - *The bystander effect/cellular communication.*

  - *A significant transcriptomic modulation for 30 genes in intracranial tumor tissue following spatial fractionation techniques, undetected in normal tissue→ mainly related to the regulation of cell cycle and to immune/inflammatory response.*

x-rays MBRT: possible transfer from synchrotrons to cost-effective equipment

IMNC + Campus d'Orsay + INSERM U836

Radiobiology platform (Institut Curie)

Synchrotron → low cost equipment

- Feasibility evaluation: modification of the irradiator (patent)
- Biological studies → understand the involved mechanisms (starting Autumn)

Radiotherapy: modeling biological response

Tumor control probability

Normal tissue complication probability

Physical dose → **Biological dose**

Biological effect of the radiation

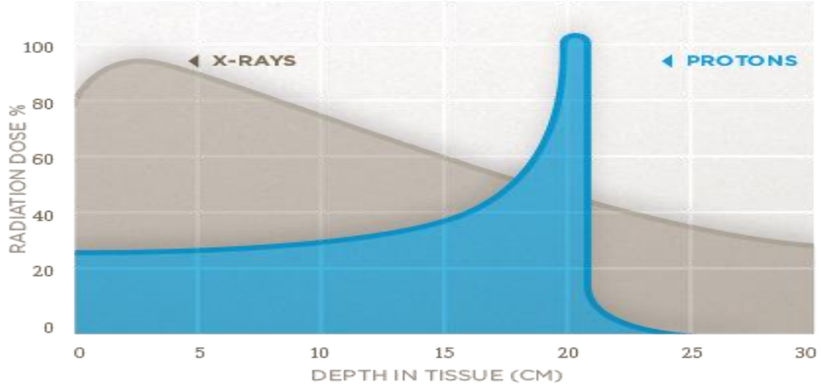
Physical parameters of irradiation

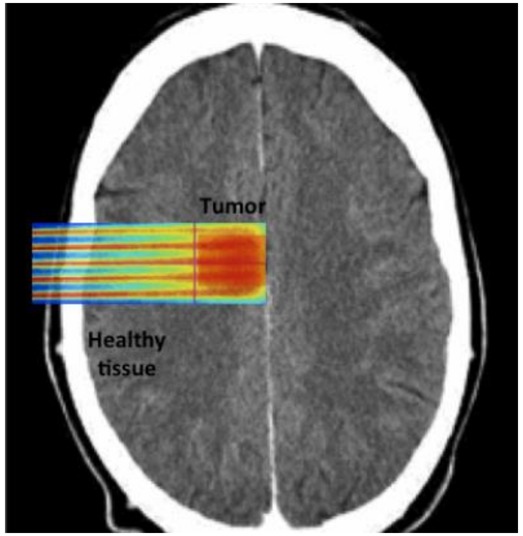
Type of radiation
Beam energy
Delivery mode: dose rate, spatial and temporal distributions, field size, etc.

Tumor type
Tumor microenviroment
Genetics

Biological factors

Proton minibeam radiation therapy

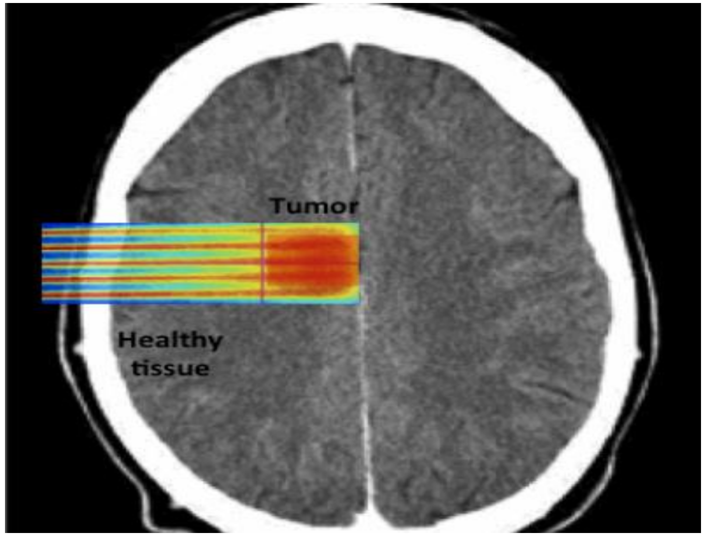


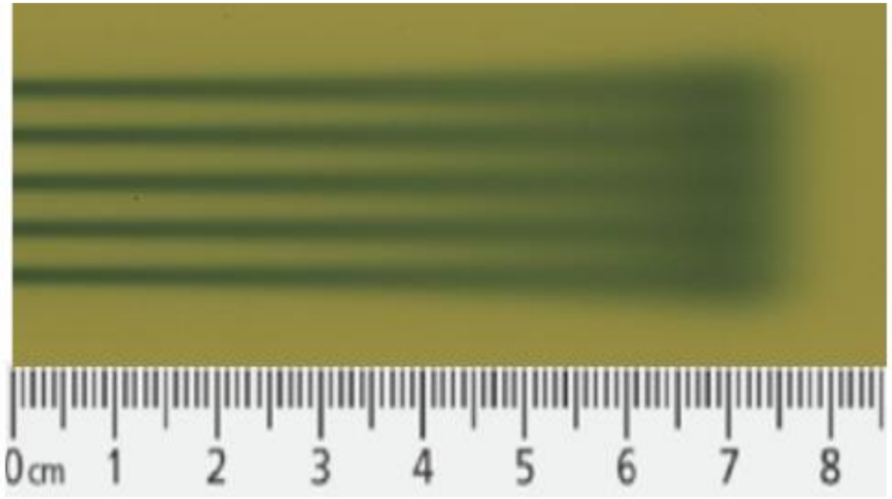


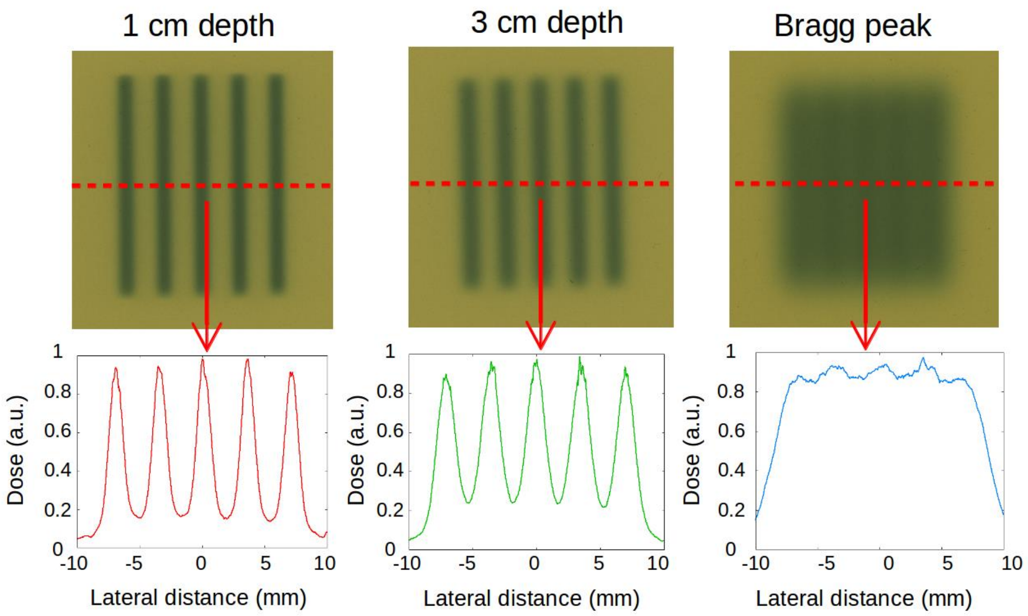
❖ **In a recent work:** Monte Carlo **proof of concept** suggested a **possible way to generate minibeams of protons** and highlithted advantages of this approach [Prezado 2013] :

- ✓ Spatial fractionation in healthy tissue
- ✓ Homogeneous distribution at the Bragg peak location

Implementation at the Proton Therapy Center Orsay







- **Spatial fractionation** of the dose in the **normal tissue** beyond the Bragg peak

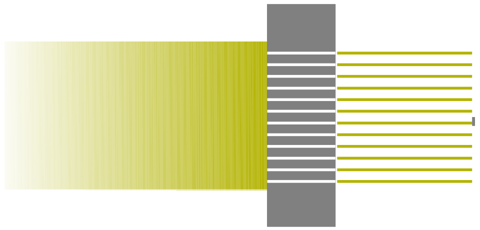
- **Quasi-homogeneous** dose distribution at the **Bragg peak location** due to multiple Coulomb scattering in depth

Potential renewed use of very heavy ions for therapy

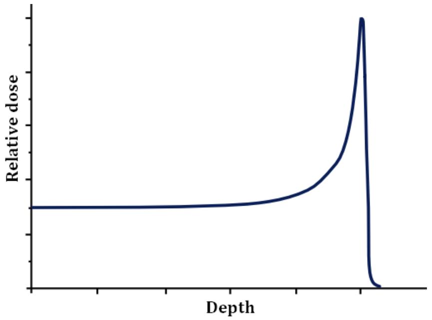
- Very heavy ions (Ne or heavier) used in the past, very effective for the treatment of hypoxic/resistant tumors (Castro 1994)
- However abandoned due to important side effects in normal tissues

<u>**Combination**</u>: MBRT + heavy ions therapy

→ **MBRT**: increase healthy tissue sparing
→ **Heavy ions:** increase tumour cells killing capacity



+



C. Peucelle et al, submitted Med. Phys.

Very heavy electrons for therapy

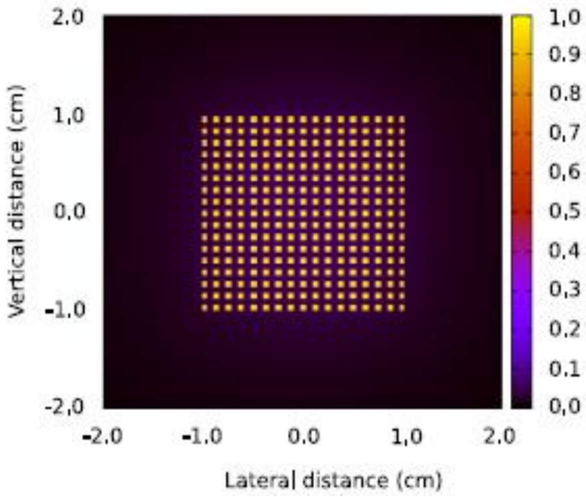
E ~300 MeV At hospitals E ~ 2 – 25 MeV

Potential clinical advantages that can be investigated:

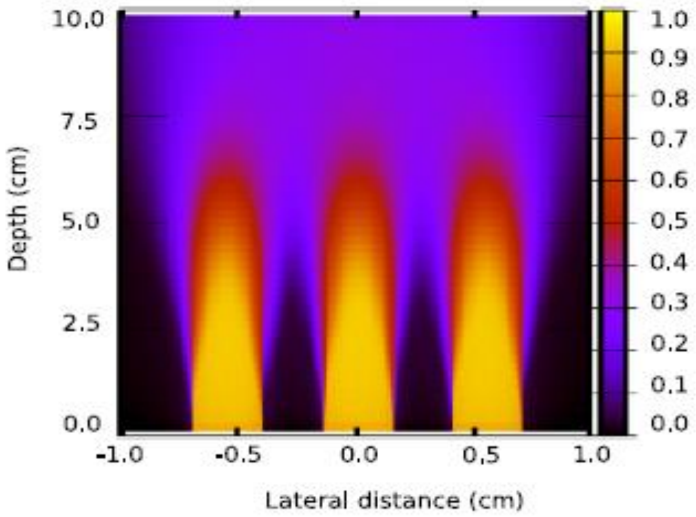
-Lateral electromagnetic scanning could have certain clinical advantages that are not possible by using photon beams. This can be advantageous for image-guided energy- and intensity modulated radiation therapy

- a possible gain in relative biological effectiveness (RBE) might be observed.

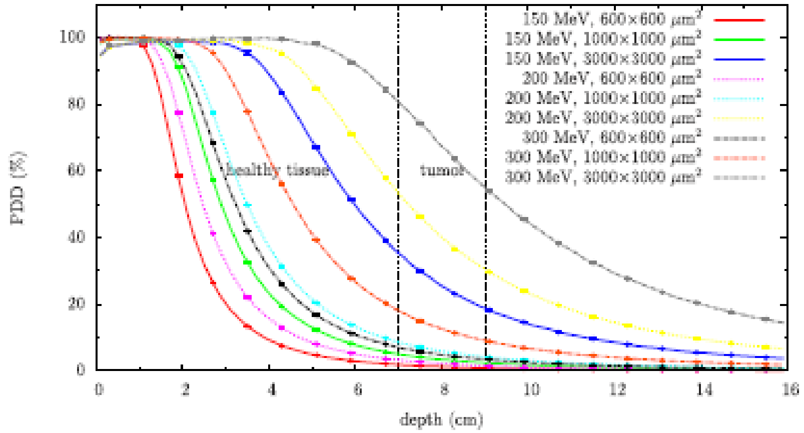
High energy electron grid therapy: colaboration with LAL



View of the grid



2D dose distributions



For a human head 250-300 MeV are required

Martinez & Prezado, Med. Phys. 2015

Technical implementation– colaboration with LAL

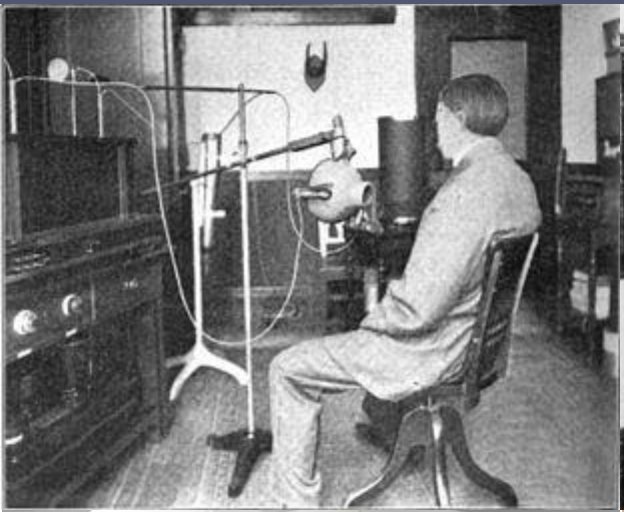
Conclusions

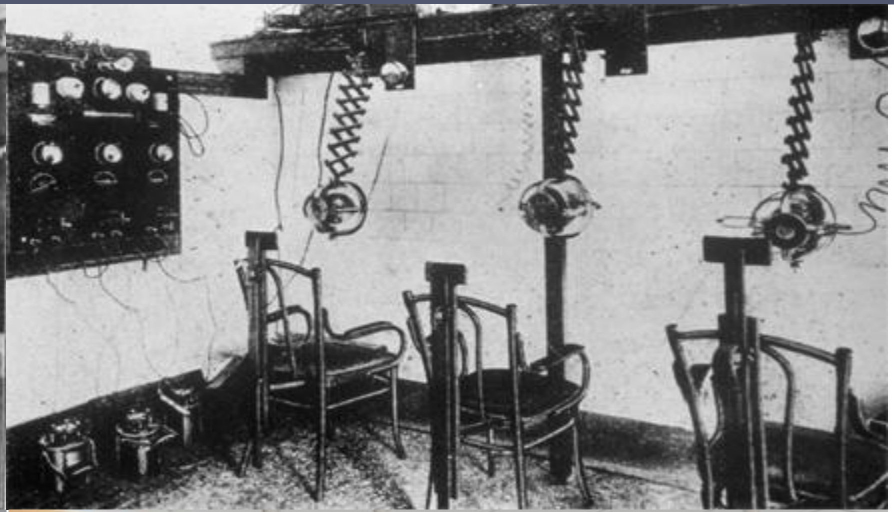
- We are still far away from having found the optimum way to use ionizing radiation for therapy

- Some relevant radiobiological effects/mechanisms only recently explored

- Physics paramaters of the irradiation can be used to model the biological response – to improve treatment outcome

- Advancements in radiotherapy require a interdisciplinary approach





Thank you for your attention

prezado@imnc.in2p3.fr